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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/390,634	09/07/1999	PAUL J. PRICE	0942.4190002	7270

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[REDACTED] EXAMINER

WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	T [REDACTED]

DATE MAILED: 03/12/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/390,634	PRICE ET AL.
	Examiner	Art Unit
	Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 21 November 2001.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 89-126 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 89-126 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>16</u> | 6) <input type="checkbox"/> Other: _____ |

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Continued Prosecution Application

The request filed on November 21, 2001, paper number 15, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/390,634 is acceptable and a CPA has been established. An action on the CPA follows.

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

This application is a divisional of application 08/781,772, filed January 10, 1997, now abandoned.

Applicants' amendment filed November 21, 2001, paper number 18, has been received and entered. Claims 89-126 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89-126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for culturing murine embryonic stem cell lines in a serum-

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free medium composition as set forth in the preferred embodiments of Tables 1-3 and Examples 1-5, and compositions composed thereof, does not reasonably provide enablement for culturing conditions or compositions for embryonic stem cells from other species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants point out to provide a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention and to explain why it doubts the truth or accuracy of any statement in a supporting disclosure, citing *In re Wright* and *In re Marzocchi*. Applicants argue that the Examiner has put the initial burden on Applicants to prove that the specification enables the full scope of the claimed invention. Further, Applicants argue that the mathematical calculation set forth in the advisory action demonstrating the large number of medium formulations does not in itself provide a case of non-enablement. See Applicants arguments, pages 2-5. Applicants arguments have been fully considered, but not found persuasive.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient

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amount for a *prima facie* case must be demonstrated. The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404).

The claims are broadly drawn to methods of expanding any embryonic stem (ES) cell, and compositions comprising serum-free medium and ES cells. The specification defines the term "embryonic stem cell" as a cell which can give rise to many differentiated cell types in an embryo or an adult, including the germ cells (sperm and eggs). The present art accepted supports this definition wherein an ES cell is a totipotent cell capable of contributing to all tissues of an animal including the germ cells (Nichols *et al.*, page 1341; first paragraph). The instant specification provides evidence in the working examples of an art recognized mouse embryonic stem cell, however it fails to provide evidence that totipotent embryonic stem cell capable of contributing to the germ line exist for any other animal besides the mouse. Upon review of the references pointed to by the instant specification (pages 18-19; bridging sentence) and in Applicants' previous amendments (paper number 9, pages 7-10) for support of a totipotent ES cell from other animals, it appears that none of the references provide substantive evidence that a totipotent ES cells exist other than for the mouse. It is noted that at the time of the claimed invention, the state of the art of ES cells encompassed by the claimed invention was not very well

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established. Further, the art recognized that the methods for isolating ES cells is highly unpredictable. For example, with regard to a developing embryo, Cruz *et al.* list some of the differences in early embryonic development among swine, oxen, horses, goats and sheep (page 166; Table 1). In addition, Piedrahita *et al.* observed that porcine and ovine embryos responded differently to the same treatments. Conditions that allowed production of porcine ES-like cell lines did not allow development of ovine ES-like cell lines (see Table 1, page 886, and page 888). Piedrahita *et al.* teach that culturing and isolation conditions for one species may not be suitable for culturing and isolation of embryonic stem-like cells from another species. Therefore, it would be recognized by one of skill in the art that one cannot simply extrapolate from procedures shown effective in one species to use or develop procedures for another species. As taught and demonstrated in Cruz *et al.* and Piedrahita *et al.* numerous attempts to isolate ES cells from species other than the mouse have been attempted however, demonstration that these cells are able to contribute to the germ line is awaited (summarized by Clark *et al.* page 250; second paragraph). The instant claims are extremely broad encompassing ES cells from any animal. It is noted that the specific working examples provided in the instant specification demonstrate that the instantly claimed conditions are effective for murine embryonic stem cells, however, in view of the art recognized unpredictability of culturing ES cells, there is no indication that these conditions would be effective for any other animal, nor is there a nexus between the methods used to culture/isolate murine ES cells and their effectiveness for use in culturing/isolating ES cells from any other species. Examiner recognizes that absent the existence of ES cells from

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other species the instant invention can not be directly tested, therefore has relied upon the art to demonstrate the inherent unpredictability for isolating and culturing totipotent ES cells. In view of the fact that the art recognizes that conditions for one ES cell may not be effective for the other ES cells it is maintained that the artisan would need specific and detailed guidance for each ES cell for each separate species, which the instant specification and the art of record fails to provide. The specification relies on the art to establish totipotent ES cell lines for use in the instant methods and compositions, and thus, is subject to the same limitations recognized by the art.

With regards to the amount of experimentation, given that one can not simply extrapolate conditions from one species of ES cell to another, the type of experimentation involved in developing the proper conditions for each species encompassed by the instant claims is empirical. The mathematical formulation set forth previously in the advisor action provides for the numerous permutations of conditions encompassed by the instant claims, and in view of the unpredictability of the art, there is no reasonable expectation that any of the conditions would be effective in culturing ES cells. Examiner would agree that the amount of experimentation is alone not sufficient to establish a *prima facie* case, however in the instant circumstance, due to the lack of predictability in the art for ES cells, the large breadth of conditions taught by the instant specification and encompassed by the claims represents an undue amount of experimentation with no reasonable expectation of success.

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Thus, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed, and therefore, the rejection is maintained.

Conclusion

No claim is allowed. The claims are free of the art of record because the art fails to teach serum-free conditions for the successful culturing of totipotent embryonic stem cells, in particular the specific medium conditions set forth in instant disclosure. However, the claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Patsy Zimmerman whose telephone number is (703)308-8338.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers

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must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach
AV1632